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(71) Applicant *(for all designated States except US)*: KOREA RESEARCH INSTITUTE OF CHEMICAL TECHNOLOGY [KR/KR]; #100, Jang-dong, Yuseong-gu, Daejon 305-343 (KR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SON, Jong, Chan [KR/KR]; Hanbit Apartment 131-603, #99, Oeun-dong, Yuseong-gu, Daejeon 305-333 (KR). SHIN, Seun, Shil [KR/KR]; #1402-26, Dukjin-dong 1-ga, Dukjin-gu, Jeonju-si, Jeonrabuk-do 561-190 (KR). KIM, Shin, Keol [KR/KR]; #553-34, Banghwa-2-dong, Kangseo-gu, Seoul 157-222 (KR). LEE, Chong, Kyo [KR/KR]; Hanul Apt. 107-604, Sinseong-dong, Yuseong-gu, Daejeon 305-345 (KR). KIM, Hae, Soo [KR/KR]; Seongwon Apt. 9-1301, Uhmsa-ri, Duma-myeon, Nonsan-si, Chungcheongnam-do 320-910 (KR).

(74) Agents: JANG, Seong, Ku et al.; 17th floor, KEC Building, #275-7, Yangjae-dong, Seocho-ku, Seoul 137-130 (KR).

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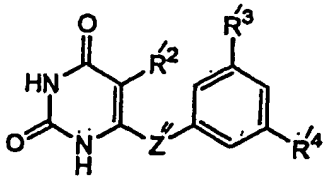
(54) Title: ANTIVIRAL 2,4-PYRIMIDINEDIONE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

2,4-pyrimidinedione derivatives of formula (I) having high antiviral activity against wild-type and mutant HIV-1 and low toxicity are useful for treating AIDS (I) wherein: R^1 is a C_{6-10} aryl or C_{3-10} heteroaryl group optionally having one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more halogen atoms, C_{3-6} cycloalkyl, cyano, nitro, hydroxy, thiohydroxy, azido, C_{1-6} alkoxy, oximino, C_{1-3} alkyloximino, O-(C_{1-6} alkyl)-substituted oximino, C-$_{1-6}$ alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, hydroxymethyl, azidomethyl, C_{1-6} alkoxymethyl, C_{1-6} acyloxymethyl, carbamoyloxymethyl, aminomethyl, N-(C_{1-3} alkyl) aminomethyl, N,N-di(C_{1-3} alkyl) aminomethyl, carboxy; C_{1-6} alkoxycarbonyl, aziridine, amino, hydroxyethylamino, cyclopropylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl) amino, trifluoroacetamido, C_{1-6} acylamido, carbamoyl, hydroxyethylcarbamoyl, cyclopropylcarbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl) carbamoyl, aminocarbamoyl, dimethylaminocarbamoyl, hydrazino, 1,1-dimethylhydrazino, imidazolyl, triazolyl and tetrazolyl; a tetrahydropyridyl or piperidyl group optionally substituted with a C_{1-6} alkyl or C_{1-6} alkoxycarbonyl group; a tetrahydropyranyl group; or a tetrahydrofuryl group; R^2 is hydrogen, halogen, nitro, cyano, C_{1-3} alkoxycarbonyl, C_{1-3} alkylamino, di(C_{1-3} alkyl) amino, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl) carbamoyl, C_{1-6} alkyl, C_{3-6} cycloalkyl or benzyl; R^3 and R^4 are each independently hydrogen, halogen, hydroxy, cyano, nitro, amino, acetamido, trifluoroacetamido, azido, C_{1-3} alkyl, C_{1-3} alkyl substituted with one or more halogen atoms, C_{1-3} alkoxycarbonyl, carbamoyl, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl) carbamoyl or C_{1-3} alkoxy; A is O or S; and Z is O, S, C=O, NH or CH_2.



(I)

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ANTIVIRAL 2,4-PYRIMIDINEDIONE DERIVATIVES AND PROCESS FOR THE PREPARATION THEREOF

Field of the Invention

The present invention relates to novel pyrimidinedione derivatives, which are useful as an antiviral agent, particularly for treating acquired immunodeficiency syndrome (AIDS), a process for the preparation thereof and a pharmaceutical composition containing same as an active ingredient.

Description of the Prior Art

Various compounds such as AZT (3'-azido-3'-deoxythymidine), DDC (2',3'-dideoxycytidine), DDI (2',3'-dideoxyinosine), D4T (3'-deoxy-2',3'-didehydrothymidine) 3TC(lamivudine), Ziagen, Nevirapine, Sustiva, Delavirdine, Indinavir, Ritonavir, Viracept, Saquinavir and Agenerase have been reported to have the ability, albeit limited, to inhibit the reproduction of AIDS virus. However, they are also known to cause undesirable side effects due to their toxicity as well as to induce the mutation of the virus, thereby increasing the resistance of the virus.

In order to minimize such problems, therefore, many attempts have been made. For example, there have been reported 2,4-pyrimidinedione derivatives having 1-alkoxymethyl substituents {J. Med. Chem., 35, 4713 (1992); J. Med. Chem., 35, 337 (1992); J. Med. Chem., 34, 1508 (1991); J. Med. Chem., 34, 1394 (1991); J. Med. Chem., 34, 349 (1991); Molecular Pharm., 39, 805 (1991); Tet. Lett., 35, 4531 (1994); J. Med. Chem., 38, 2860 (1995); Nucleosides and Nucleotides, 14, 575 (1995); J. Med. Chem., 39, 2427 (1996); J. Med. Chem., 42, 4500 (1999); EP 0,449,726 A1; EP 0,420,763 A2; USP 5,278,167; USP 5,318,972; USP 5,461,060; WO95/18109 A1; and USP 5,112,835}; 1-allyl or propargyl substituents (USP 5,747,500); and 1-cyclopentenylmethylene

substituents (USP 5,922,727). Although these compounds exhibit improved activity against human immunodeficiency virus (HIV), there exists a need to develope non-toxic compounds having even higher potency against both wild-type and mutant HIV.

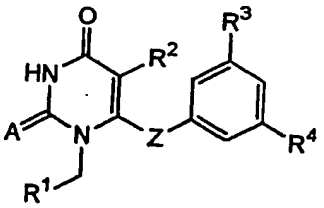
Summary of the Invention

Accordingly, it is a primary object of the present invention to provide a novel compound having superior antiviral activity against both wild-type and mutant HIV-1 as well as reduced toxicity.

It is another object of the present invention to provide a pharmaceutical composition containing same.

It is a further object of the present invention to provide a process for the preparation of said novel compound.

In accordance with one aspect of the present invention, there is provided a novel 2,4-pyrimidinedione compound of formula(I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is a C_{6-10} aryl or C_{3-10} heteroaryl group optionally having one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more halogen atoms, C_{3-6} cycloalkyl, cyano, nitro, hydroxy, thiohydroxy, azido, C_{1-6} alkoxy, oximino, C_{1-3} alkyloximino, O-(C_{1-6} alkyl)-substituted oximino, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, hydroxymethyl, azidomethyl, C_{1-6} alkoxymethyl, C_{1-6} acyloxymethyl,

carbamoyloxymethyl, aminomethyl, N-(C_{1-3} alkyl)aminomethyl, N,N-di(C_{1-3} alkyl)aminomethyl, carboxy, C_{1-6} alkoxycarbonyl, aziridine, amino, hydroxyethylamino, cyclopropylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, trifluoroacetamido, C_{1-6} acylamido, carbamoyl, hydroxyethylcarbamoyl, cyclopropylcarbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, aminocarbamoyl, dimethylaminocarbamoyl, hydrazino, 1,1-dimethylhydrazino, imidazolyl, triazolyl and tetrazolyl; a tetrahydropyridyl or piperidyl group optionally substituted with a C_{1-6} alkyl or C_{1-6} alkoxycarbonyl group; a tetrahydropyranyl group; or a tetrahydrofuryl group;

R^2 is hydrogen, halogen, nitro, cyano, C_{1-3} alkoxycarbonyl, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl)carbamoyl, C_{1-6} alkyl, C_{3-6} cycloalkyl or benzyl;

R^3 and R^4 are each independently hydrogen, halogen, hydroxy, cyano, nitro, amino, acetamido, trifluoroacetamido, azido, C_{1-3} alkyl, C_{1-3} alkyl substituted with one or more halogen atoms, C_{1-3} alkoxycarbonyl, carbamoyl, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl)carbamoyl or C_{1-3} alkoxy;

A is O or S; and

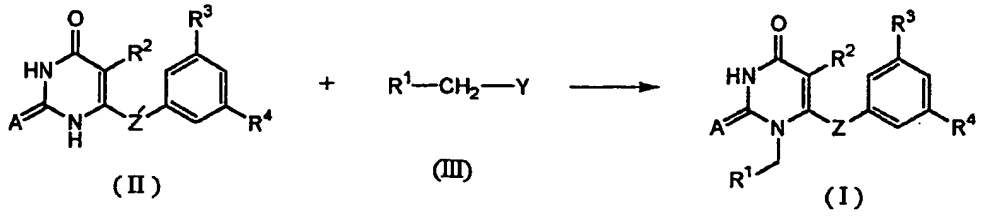
Z is O, S, C=O, NH or CH_2.

Detailed Description of the Invention

Among the compounds of formula(I) of the present invention, the preferred are those wherein R^1 is a phenyl, pyridyl or N-oxopyridyl group optionally having one or more substituents as listed in formula(I).

The 2,4-pyrimidinedione compound of formula(I) may be prepared by coupling a compound of formula(II) with a compound of formula(III), as shown in the Reaction Scheme A:

Reaction Scheme A



wherein:

R^1, R^2, R^3, R^4, A and Z have the same meanings as defined in formula(I) above;

Z' is same as Z with the proviso that when A is oxygen, it can be a acetamido group; and

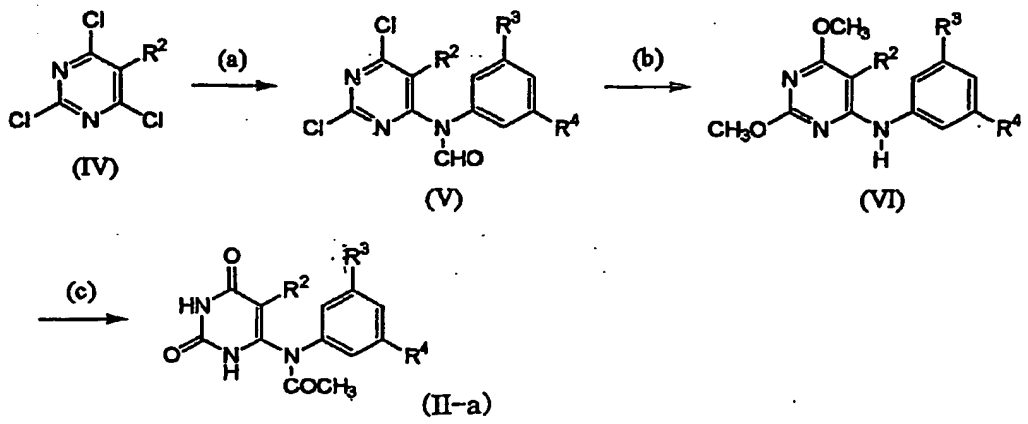
Y is a suitable leaving group, e.g., halogen, methanesulfonyl, toluenesulfonyl or trifluoromethanesulfonyl.

In Reaction Scheme A, the above reaction may be conducted in a solvent in the presence of a base at a temperature ranging from -10 to 100°C, wherein the molar ratio of the compound of formula(II) to the compound of formula(III) may range from 1:0.8 to 1:1.2. Representative examples of the base include lithium hydride, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate and the like. Suitable for use in this reaction is a polar solvent such as acetonitrile, hexamethylphosphoramide(HMPA), dimethylsulfoxide(DMSO) and dimethylformamide(DMF).

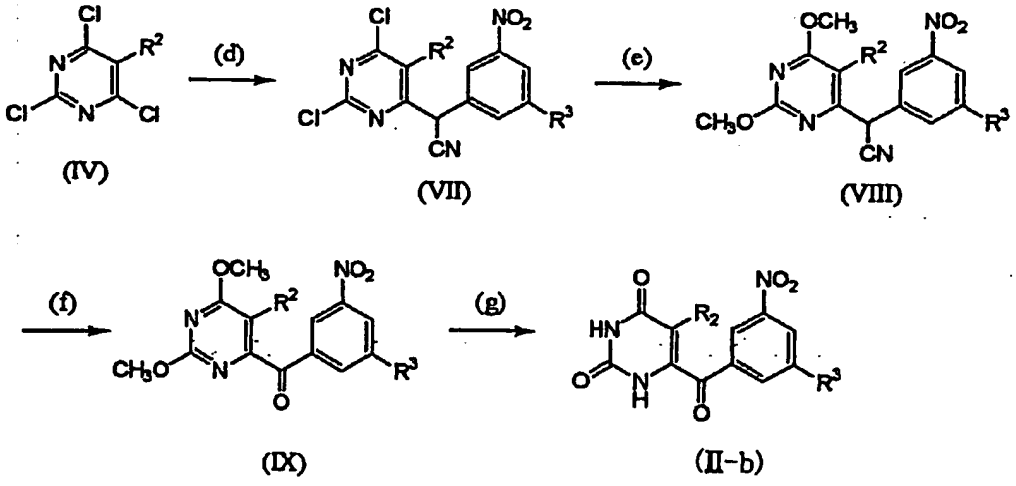
The compounds of formula(II) may in some cases be prepared in accordance with the procedure disclosed in USP 5,747,500. Alternatively, the compounds of formula(II) may be advantageously prepared in some special cases by the procedure illustrated in Reaction Scheme B:

Reaction Scheme B

Method (i): Useful when A is O and Z' is acetamido



Method (ii): Useful when A is O, Z' is C=O and R^3(or R^4) is NO_2



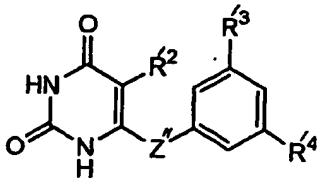
wherein, R^2, R^3 and R^4 have the same meanings as defined in formula(I).

In accordance with the method (i) in Reaction Scheme B, a compound of formula(IV) which may be prepared by way of a known method disclosed in, e.g., Ber., 52B, 869 (1919) and J. Med. Chem., 7, 808 (1964), is subjected to a coupling reaction with an arylformamide derivative in a polar solvent, e.g., dimethylformamide, in the presence of a strong base, e.g., sodium hydride, under a nitrogen atmosphere to provide a compound of formula(V) (Step (a)). The compound of formula(V) is reacted with sodium methoxide in methanol to give a compound of formula(VI) (Step (b)). Then, the compound of formula(VI) is demethylated and acetylated by the action of acetylbromide to provide a compound of formula(II-a) (Step (c)).

In the method (ii) of Reaction Scheme B, the compound of formula (IV) is reacted with a arylacetonitrile derivative in a polar solvent, e.g., dimethylformamide, in the presence of a base, e.g., sodium hydride, to provide a compound of formula(VII) (Step (d)), which is reacted with sodium methoxide in methanol to give a compound of formula(VIII) (Step (e)). Thereafter, the compound of formula(VIII) is reacted with a base, e.g., sodium hydride, in a polar solvent, e.g., dimethylformamide, in the presence of oxygen to provide a compound of formula(IX) (Step (f)), which is hydrolyzed with an acid, e.g., hydrochloric acid, to provide a compound of formula(II-b) (Step (g)).

Each of the compounds of formula(II-a) and (II-b) may be converted to one of the compounds of formula(II) containing various substituents via further reactions.

In this regard, in accordance with another aspect of the present invention, there is provided a compound of formula(II):



(II)

wherein:

R'^2 is ethyl or isopropyl;

R'^3 is nitro, amino, acetamido, trifluoroacetamido or C_{1-3} alkoxycarbonyl;

R'^4 is methyl or halogen; and

Z" is C=O, NH or acetamido.

Exemplary compounds of formula(I) of the present invention which can be prepared in accordance with the methods described above are listed in the following Table 1:

Table 1

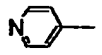
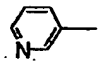
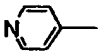
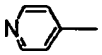
Comp.	A	Z	R^1	R^2	R^3	R^4
1	O	C=O		Isopropyl	CH_3	CH_3
2	O	C=O		Isopropyl	CH_3	CH_3
3	O	C=O		Isopropyl	CH_3	CH_3
4	O	C=O		Ethyl	CH_3	CH_3
5	O	C=O		Ethyl	CH_3	CH_3
6	O	C=O		Ethyl	CH_3	CH_3
7	O	C=O		Isopropyl	CH_3	F
8	O	C=O		Isopropyl	CH_3	F
9	O	C=O		Isopropyl	CH_3	F

Table 1 (Continued)

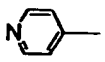
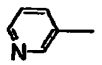
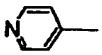
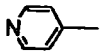
Comp.	A	Z	R^1	R^2	R^3	R^4
10	O	C=O		Ethyl	CH_3	F
11	O	C=O		Ethyl	CH_3	F
12	O	C=O		Ethyl	CH_3	F
13	O	C=O		Isopropyl	F	F
14	O	C=O		Isopropyl	F	F
15	O	C=O		Isopropyl	F	F
16	O	C=O		Ethyl	F	F
17	O	C=O		Ethyl	F	F
18	O	C=O		Ethyl	F	F

Table 1 (Continued)

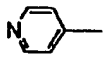
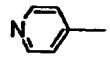
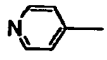
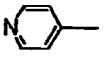
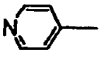
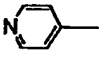
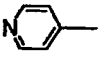
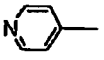
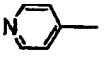
Comp.	A	Z	R^1	R^2	R^3	R^4
19	O	C=O		Isopropyl	Cl	Cl
20	O	C=O		Ethyl	Cl	Cl
21	O	C=O		Isopropyl	CH_3	Cl
22	O	C=O		Isopropyl	CH_2F	CH_3
23	O	C=O		Ethyl	CH_2F	CH_3
24	O	O		Isopropyl	CH_3	CH_3
25	O	O		Ethyl	CH_3	CH_3
26	O	S		Isopropyl	Cl	Cl
27	O	S		Isopropyl	CH_3	CH_3

Table 1 (Continued)

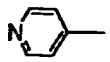
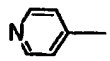
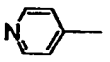
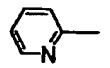
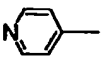
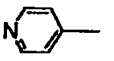
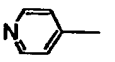
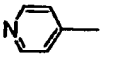
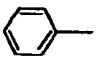
Comp.	A	Z	R^1	R^2	R^3	R^4
28	O	S		Ethyl	CH_3	CH_3
29	O	C=O		Isopropyl	CF_3	CF_3
30	O	C=O		Ethyl	CF_3	CF_3
31	O	C=O		Isopropyl	CF_3	CF_3
32	O	C=O		Isopropyl	CH_3	H
33	O	C=O		Ethyl	CH_3	H
34	O	C=O		Isopropyl	H	H
35	O	C=O		Ethyl	H	H
36	O	C=O		Isopropyl	CH_3	CH_3

Table 1 (Continued)

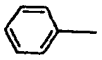
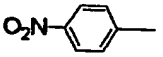
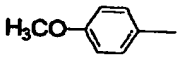
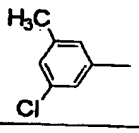
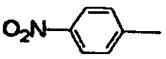
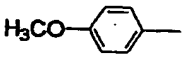
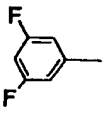
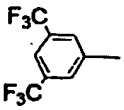
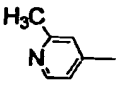
Comp.	A	Z	R^1	R^2	R^3	R^4
37	O	C=O		Ethyl	CH_3	CH_3
38	O	C=O		Isopropyl	CH_3	CH_3
39	O	C=O		Isopropyl	CH_3	CH_3
40	O	C=O		Isopropyl	CH_3	CH_3
41	O	C=O		Ethyl	CH_3	CH_3
42	O	C=O		Ethyl	CH_3	CH_3
43	O	C=O		Isopropyl	CH_3	CH_3
44	O	C=O		Isopropyl	CH_3	CH_3
45	O	C=O		Isopropyl	CH_3	CH_3

Table 1 (Continued)

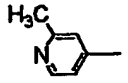
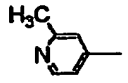
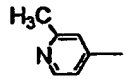
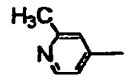
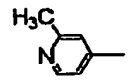
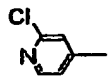
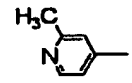
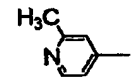
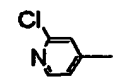
Comp.	A	Z	R^1	R^2	R^3	R^4
46	O	C=O		Isopropyl	CH_3	F
47	O	C=O		Isopropyl	CH_3	Cl
48	O	C=O		Isopropyl	Cl	Cl
49	O	C=O		Isopropyl	CH_2F	CH_3
50	O	C=O		Isopropyl	CH_3	H
51	O	C=O		Isopropyl	CH_3	CH_3
52	O	C=O		Ethyl	CH_3	CH_3
53	O	C=O		Ethyl	CH_3	F
54	O	C=O		Ethyl	CH_3	CH_3

Table 1 (Continued)

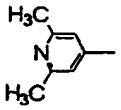
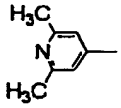
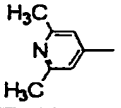
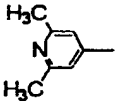
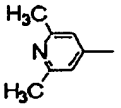
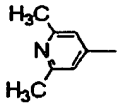
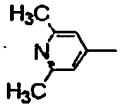
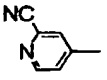
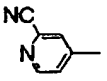
Comp.	A	Z	R^1	R^2	R^3	R^4
55	O	C=O		Isopropyl	CH_3	CH_3
56	O	C=O		Isopropyl	F	F
57	O	C=O		Isopropyl	Cl	Cl
58	O	C=O		Isopropyl	CH_2F	CH_3
59	O	C=O		Isopropyl	Cl	CH_3
60	O	C=O		Ethyl	CH_3	CH_3
61	O	C=O		Ethyl	F	F
62	O	C=O		Isopropyl	CH_3	CH_3
63	O	C=O		Isopropyl	CH_3	Cl

Table 1 (Continued)

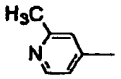
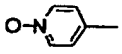
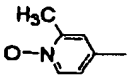
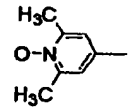
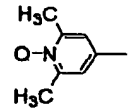
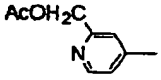
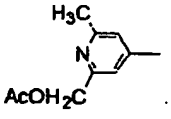
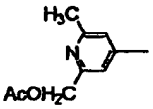
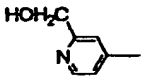
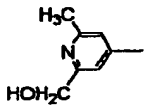
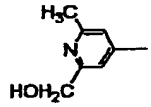
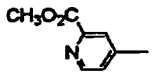
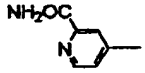
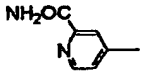
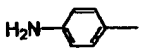
Comp.	A	Z	R^1	R^2	R^3	R^4
64	O	C=O		Isopropyl	CH_3	NO_2
65	O	C=O		Isopropyl	CH_3	NO_2
66	O	NH		Isopropyl	CH_3	CH_3
67	O	NH		Ethyl	CH_3	CH_3
68	O	C=O		Isopropyl	CH_3	CH_3
69	O	C=O		Isopropyl	CH_3	CH_3
70	O	C=O		Isopropyl	CH_3	CH_3
71	O	C=O		Isopropyl	CH_3	Cl
72	O	C=O		Isopropyl	CH_3	CH_3
73	O	C=O		Isopropyl	CH_3	CH_3

Table 1 (Continued)

Comp.	A	Z	R^1	R^2	R^3	R^4
74	O	C=O		Isopropyl	CH_3	Cl
75	O	C=O		Isopropyl	CH_3	CH_3
76	O	C=O		Isopropyl	CH_3	CH_3
77	O	C=O		Isopropyl	CH_3	Cl
78	O	C=O		Isopropyl	CH_3	CH_3
79	O	C=O		Isopropyl	CH_3	CH_3
80	O	C=O		Isopropyl	CH_3	Cl
81	O	C=O		Isopropyl	CH_3	CH_3

Furthermore, the present invention encompasses, within its scope, pharmaceutically acceptable salts of the 2,4-pyrimidinedione compounds of formula(I). Suitable pharmaceutically acceptable salts of the compounds of formula(I) possessing strong antiviral activity against wild-type and mutant HIV-1 may include alkali or alkaline earth metal salts, e.g., sodium, potassium, magnesium and calcium salts thereof.

The present invention also includes within its scope pharmaceutical compositions comprising one or more of the compounds of formula(I) or their above-mentioned salts as the active ingredient, in association with pharmaceutically acceptable carriers, excipients or other additives, if necessary.

The pharmaceutical compositions of the invention may be formulated for administration orally or by injection. The composition for oral administration may take various forms such as tablets and gelatin capsules, which may contain conventional additives such as a diluent (e.g., lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and glycine), a lubricant (e.g., silica, talc, stearic acid or its magnesium and calcium salts and polyethylene glycol). In the case of the tablet form, the composition may further comprise a binder (e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose and polyvinyl pyrrolidone) and optionally a disintegrant (e.g., starch, agar and alginic acid or its sodium salt), absorbent, colorant, flavor, sweetener and the like. The composition for injection may be an isotonic solution or a suspension.

The composition may be sterilized and/or contain an adjuvant such as a preservative, stabilizer, wetting agent, emulsifier, a salt for controlling an osmotic pressure and/or a buffer solution, and other pharmaceutically effective materials.

The pharmaceutical compositions can be prepared by a conventional mixing, granulating or coating method and may

contain preferably about 0.1 to 75 %, more preferably about 1 to 50 % of the active ingredient of this invention. The unit dosage of the composition suitable for administering a person weighing about 50 to 70 kg may contain about 10 to 200mg of the active ingredient.

The following Preparations and Examples are given for the purpose of illustration only and are not intended to limit the scope of the invention.

In the Preparations and Examples, unless otherwise specified, the evaporation was conducted under reduced pressure, preferably under a pressure ranging from about 15 to 100 mmHg.

Preparations

The compounds of formula(II) having the structures (A) to (U), (II-a-1), (II-a-2) and (II-b-1) shown in Table 2 together with their melting points and NMR data were used in preparing respective compounds of formula(I) of the present invention.

Preparations 1 to 21

Each of the compounds having the specified structures (A) to (U) was prepared in accordance with the procedure described in USP 5,747,500.

Preparation 22 : Synthesis of 5-isopropyl-6-(3',5'-dimethylphenylacetamido)-2,4-pyrimidinedione (Compound (II-a-1))

Step 1) Synthesis of 2,4-dichloro-5-isopropyl-6-(3',5'-dimethylphenylformylamido)pyrimidine

To a magnetically stirred DMF solution (80ml) of 3,5-dimethylformaniline (8.94g, 60mmol) cooled in an ice bath, 60% sodium hydride dispersion (2.88g, 72mmol) was added portionwise under a nitrogen atmosphere. After 10min, 5-isopropyl-2,4,6-trichloropyrimidine (16.2g, 72mmol) was added thereto and the reaction mixture was allowed to warm

to room temperature, followed by stirring for 24hr. Ether was then added to the reaction mixture, and the organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - ether:hexane=1:15) to afford 3.3g (yield 17%) of the title compound as a white solid.

M.p. : 151 to 153 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12-1.24(6H, m), 2.30(6H, s), 3.22(1H, m), 6.72(2H, s), 6.96(1H, s), 8.70(1H, s)

m/z(EI) 338(M^+).

Step 2) Synthesis of 2,4-dimethoxy-5-isopropyl-6-(3',5'-dimethylphenylamino)pyrimidine

Sodium (1.02g, 44mmol) was added portionwise to a stirred anhydrous methanol (40ml) at room temperature under a nitrogen atmosphere to prepare sodium methoxide solution. The compound obtained in Step 1) (3g, 8.88mmol) was added to the solution and the mixture was refluxed for 4hr. The reaction mixture was allowed to cool to room temperature and neutralized with excess ammonium chloride. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - ethyl acetate:hexane=1:15) to afford 2.6g (yield 97%) of the title compound as a white solid.

M.p. : 126 to 127 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.31(6H, d, J=7.1Hz), 2.31(6H, s), 3.12(1H, m), 3.92(3H, s), 3.93(3H, s), 6.44(1H, s), 6.70(1H, s), 7.21(2H, s)

m/z(EI) 301(M^+).

Step 3) Synthesis of 5-isopropyl-6-(3',5'-dimethylphenylacetamido)-2,4-pyrimidinedione

The compound obtained in Step 2) (2.6g, 8.6mmol) was refluxed with acetyl bromide (30ml) for 19hr. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The resulting

residue was purified by flash chromatography (eluent - ethyl acetate:hexane=2:1) to afford 2.6g (yield 96%) of the title compound as a white solid.

Preparation 23 : Synthesis of 5-ethyl-6-(3',5'-dimethylphenylacetamido)-2,4-pyrimidinedione (Compound (II-a-2))

The procedure of Preparation 22 was repeated using 5-ethyl-2,4,6-trichloropyrimidine in place of 5-isopropyl-2,4,6-trichloropyrimidine to prepare the title compound.

Preparation 24 : Synthesis of 5-isopropyl-6-(3'-nitro-5'-methylbenzoyl)-2,4-pyrimidinedione (Compound (II-b-1))

Step 1) Synthesis of 2,4-dichloro-5-isopropyl-6-(α-cyano-3'-nitro-5'-methylbenzyl)pyrimidine

To a magnetically stirred DMF solution (30ml) of 3-nitro-5-methylphenylacetonitrile (2.64g, 15mmol) and 5-isopropyl-2,4,6-trichloropyrimidine (4.05g, 18mmol) cooled in an ice bath, 60% sodium hydride dispersion (1.15g, 30mmol) was added portionwise under a nitrogen atmosphere. After stirring for 2hr, the reaction mixture was allowed to warm to room temperature and stirred for 16hr. The reaction mixture was then neutralized with aqueous ammonium chloride and ethyl ether was added thereto. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - ethyl acetate:hexane=1:4) to afford 3.99g (yield 73%) of the title compound as a white solid.
M.p. : 124 to 125 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.23(3H, d, J=7.2Hz), 1.38(3H, d, J=7.2Hz), 2.51(3H, s), 3.34(1H, m), 5.60(1H, s), 7.57(1H, s), 7.99(1H, s), 8.07(1H, s)
m/z(EI) 365(M^+).

Step 2) Synthesis of 2,4-dimethoxy-5-isopropyl-6-(α-cyano-3'-nitro-5'-methylbenzyl)pyrimidine

To a stirred anhydrous methanol solution (60ml) of the compound obtained in Step 1) (3.65g, 10mmol), sodium methoxide (3.24g, 60mmol) was added at room temperature under a nitrogen atmosphere and refluxed for 24hr. The reaction mixture was then allowed to cool to room temperature and neutralized with excess ammonium chloride. After removing the solvent, the resulting residue was purified by flash chromatography (eluent - ether:hexane=1:3) to afford 1.8g (yield 50%) of the title compound as a light yellow solid.

M.p. : 134 to 135 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.15(3H, d, J=6.7Hz), 1.20(3H, d, J=6.7Hz), 2.49(3H, s), 3.05(1H, m), 4.00(3H, s), 4.01(3H, s), 5.48(1H, s), 7.62(1H, s), 8.00(2H, s)

m/z(EI) 356(M^+).

Step 3) Synthesis of 2,4-dimethoxy-5-isopropyl-6-(3'-nitro-5'-methylbenzoyl)pyrimidine

To a stirred DMF solution (20ml) of the compound obtained in Step 2) (1.7g, 4.7mmol), 60% sodium hydride dispersion (283mg, 7.1mmol) was added at room temperature under a nitrogen atmosphere. The mixture was then stirred in the presence of oxygen. After 5hr, the reaction mixture was neutralized with ammonium chloride and ethyl ether was added thereto. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - dichloromethane:hexane=97:3) to afford 1.03g (yield 62%) of the title compound as a white solid.

M.p. : 111 to 112 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.21(6H, d, J=6.9Hz), 2.54(3H, s), 2.88(1H, m), 3.93(3H, s), 4.09(3H, s), 8.05(1H, s), 8.27(1H, s), 8.44(1H, s)

m/z(EI) 345(M^+).

Step 4) Synthesis of 5-isopropyl-6-(3'-nitro-5'-methylbenzoyl)-2,4-pyrimidinedione

The compound obtained in Step 3) (630mg, 1.8mmol) was refluxed with conc. hydrochloric acid (6ml) for 4hr and the reaction mixture was allowed to cool to room temperature. The precipitate was then collected, washed with distilled water and hexane, and dried to give 560mg (yield 98%) of the title compound as a white solid.

Table 2

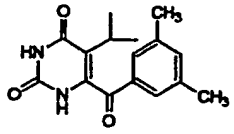
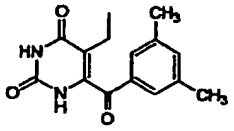
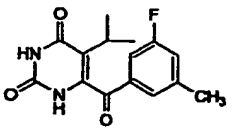
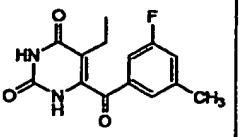
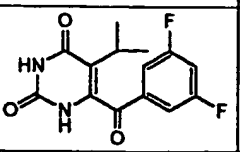
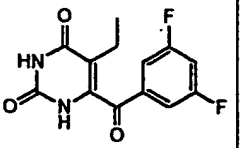
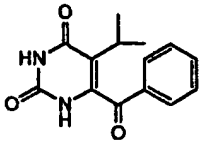
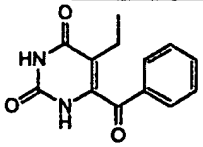
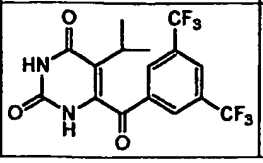
Prep. No.	Comp.	Structure	M.p.(℃)	^{1}H-NMR
1	(A)		238-239	(200MHz, $CDCl_3/CD_3OD$) δ : 1.16(6H, d, J=6.9Hz), 2.35-2.49(7H, m), 7.35(2H, s). 7.53(2H, s).
2	(B)		249-250	(200MHz, $CDCl_3/CD_3OD$) δ : 0.97(3H, t, J=7.4Hz), 2.17(2H, q, J=7.4Hz), 2.39(6H, s), 7.32(1H, s), 7.50(2H, s).
3	(C)		251-252	(200MHz, $CD_3OD/DMSO-d_6$) δ : 1.36(6H, d, J=6.9Hz), 2.38(1H, m), 2.46(3H, s), 7.26(1H, d, J=9.0Hz), 7.43(1H, d, J=8.4Hz), 7.52(1H, s).
4	(D)		235-236	(200MHz, $CD_3OD/DMSO-d_6$) δ : 0.99(3H, t, J=7.4Hz), 2.17(2H, q, J=7.4Hz), 2.50(3H, s), 7.44(1H, d, J=9.4Hz), 7.59(1H, d, J=8.8Hz), 7.70(1H, m).
5	(E)		233-234	(200MHz, $CDCl_3/CD_3OD$) δ : 1.06(6H, d, J=7.0Hz), 2.32(1H, m), 7.07(1H, m), 7.25-7.38(2H, m).
6	(F)		211-212	(200MHz, $CDCl_3/CD_3OD$) δ : 0.88(3H, t, J=7.3Hz), 2.06(2H, q, J=7.3Hz), 7.06(1H, m); 7.32-7.37(2H, m)
7	(G)		220-221	(200MHz, CD_3OD) δ : 1.16(6H, d, J=7.0Hz), 2.45(1H, m), 7.61-8.02(5H, m)
8	(H)		218-219	(200MHz, CD_3OD) δ : 0.98(3H, t, J=7.5Hz), 2.17(2H, q, J=7.5Hz), 7.58-8.03(5H, m)
9	(I)		220-221	(200MHz, $CDCl_3/CD_3OD$) δ : 1.17(6H, d, J=6.8Hz), 2.39(1H, m), 8.21(1H, s), 8.37(2H, s).

Table 2 (Continued)

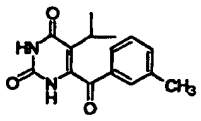
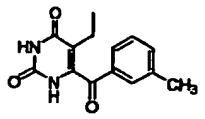
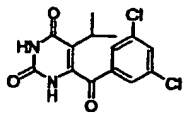
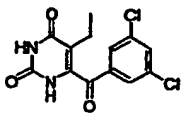
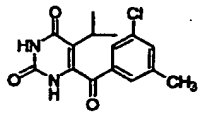
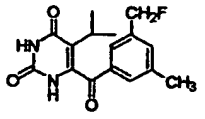
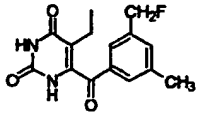
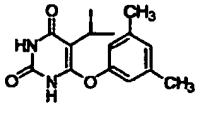
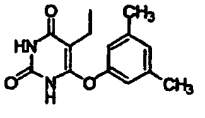
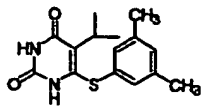
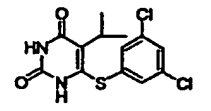
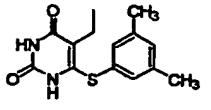
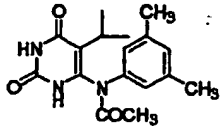
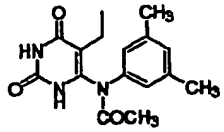
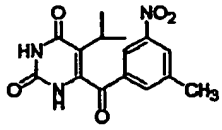
Prep. No.	Comp.	Structure	M.p.(℃)	^{1}H-NMR
10	(J)		227-228	(200MHz, $CDCl_3/CD_3OD$) δ : 1.13(6H, d, J=7.0Hz), 2.35-2.50(4H, m), 7.42-7.72(4H, m), 9.82(1H, s).
11	(K)		236-237	(200MHz, $CDCl_3/CD_3OD$) δ : 0.97(3H, t, J=7.5Hz), 2.18(2H, q, J=7.5Hz), 2.44(3H, s), 7.28-7.71(4H, m), 9.70(1H,s).
12	(L)		252-253	(200MHz, $CDCl_3/CD_3OD$) δ : 1.11(6H, d, J=6.9Hz), 2.33(1H, m), 7.61-7.73(3H, m).
13	(M)		242-243	(200MHz, $CDCl_3/CD_3OD$) δ : 0.90(3H, t, J=7.5Hz), 2.07(2H, q, J=7.5Hz), 7.59(1H, t, J=1.8Hz), 7.67(2H, d, J=1.8Hz).
14	(N)		254-255	(200MHz, $CDCl_3/CD_3OD$) δ : 1.17(6H, d, J=6.9Hz), 2.25-2.45(4H, m), 7.50-7.71(3H, m).
15	(O)		218-219	(200MHz, $CDCl_3/CD_3OD$) δ : 1.10(6H, d, J=6.9Hz), 2.32-2.52(4H, m), 5.41(2H, d, J=47.0Hz), 7.51-7.70(3H, m), 9.15(1H, s), 9.66(1H, s).
16	(P)		224-225	(200MHz, $CDCl_3/CD_3OD$) δ : 0.98(3H, t, J=7.4Hz), 2.16(2H, q, J=7.4Hz), 2.47(3H, s), 5.43(2H, d, J=47.2Hz), 7.54-7.71(3H, m).
17	(Q)		229-230	(200MHz, CD_3OD) δ : 1.20(6H, d, J=7.1Hz), 2.33(6H, s), 3.35(1H, m), 6.64(2H, s), 6.83(1H, s).
18	(R)		221-222	(200MHz, CD_3OD) δ : 0.90(3H, t, J=7.4Hz), 2.17-2.25(8H, m), 6.62(2H, s), 6.78(1H, s).

Table 2 (Continued)

Prep. No.	Comp.	Structure	M.p.(℃)	^{1}H-NMR
19	(S)		225-226	(200MHz, $CDCl_3$) δ : 1.34(6H, d, J=7.0Hz), 2.35(6H, s), 3.11(1H, m), 7.14(1H, s), 7.16(2H, s), 9.30(1H, s).
20	(T)		224-225	(200MHz, DMSO-d_6) δ : 1.17(6H, d, J=6.8Hz), 3.22(1H, m), 7.42(2H, s), 7.56(1H, s), 10.96(1H, s), 11.18(1H, s).
21	(U)		224-225	(200MHz, $CDCl_3$) δ : 1.14(3H, t, J=7.5Hz), 2.36(6H, s), 2.55(2H, q, J=7.5Hz), 7.06(1H, s), 7.16-7.26(3H, m), 9.04(1H, s)
22	(II-a-1)		224-226	(200MHz, $CDCl_3$) δ : 1.12-1.33(6H, m), 2.02-2.15(3H, m), 2.31(6H, s), 2.90(1H, m), 6.99(3H, s)
23	(II-a-2)		238-239	(200MHz, $CDCl_3$) δ : 0.93(3H, t, J=7.5Hz), 2.05-2.15(3H, m), 2.24-2.40(8H, m), 6.94-6.99(3H, m)
24	(II-b-1)		254-256	(200MHz, $CDCl_3$/CD_3OD) δ : 1.12(6H, d, J=7.0Hz), 2.40(1H, m), 2.54(3H, s), 8.11(1H, s), 8.37(1H, s), 8.49(1H, s)

Example 1 : Synthesis of 1-(4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 1)

To a magnetically stirred DMF solution (5ml) of compound (A) obtained in Preparation 1 (286mg, 1mmol) maintained at room temperature, were added anhydrous potassium carbonate (276mg, 2mmol), lithium iodide (134mg, 1mmol), and 4-picolyl chloride hydrochloride (164mg, 1mmol), in this order. After stirring for 16hr, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - ethyl acetate:hexane=3:1) to afford 120mg (yield 32%) of the title compound as a white solid.

M.p. : 264 to 265 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.30-2.40(7H, m), 4.66(1H, d, J=16.3Hz), 4.88(1H, d, J=16.3Hz), 6.98-7.36(5H, m), 8.41-8.44(2H, m), 9.91(1H, s)

m/z(EI) 377(M^+).

Example 2 : Synthesis of 1-(3'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 2)

The procedure of Example 1 was repeated using 3-picolyl chloride hydrochloride in place of 4-picolyl chloride hydrochloride to prepare the title compound.

M.p. : 179 to 180 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.9Hz), 1.22(3H, d, J=6.9Hz), 2.20-2.38(7H, m), 4.71(1H, d, J=16.0Hz), 4.93(1H, d, J=16.0Hz), 7.09-7.56(5H, m), 8.29-8.43(2H, m), 10.18(1H, s)

m/z(EI) 377(M^+).

Example 3 : Synthesis of 1-(2'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 3)

The procedure of Example 1 was repeated using 2-picolyl

chloride hydrochloride in place of 4-picolyl chloride hydrochloride to prepare the title compound.

M.p. : 214 to 215 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.20-2.40(7H, m), 4.77(1H, d, J=16.8Hz), 5.16(1H, d, J=16.8Hz), 7.01-7.48(6H, m), 8.36(2H, m), 9.90(1H, s)

m/z(EI) 377(M^+).

Examples 4 to 65

The procedure of Example 1 was repeated to obtain the 2,4-pyrimidinedione derivatives of Examples 4-65 shown in Table 3.

Table 3

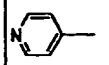
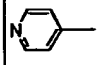
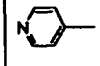
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
4	O	C=O		Ethyl	CH_3	CH_3	0.97(3H, t, J=7.3Hz), 2.05(1H, m), 2.20-2.35(7H,m). 4.70(1H, d, J=16.4Hz), 4.90(1H, d, J=16.4Hz), 6.98-7.01(2H, m), 7.27(1H, s), 7.34(2H, s), 8.41-8.44(2H, m), 9.25(1H, s).	267-268
5	O	C=O		Ethyl	CH_3	CH_3	0.95(3H, t, J=7.3Hz), 2.02(1H, s), 2.20-2.40(7H, m), 4.72(1H, d, J=16.4Hz), 4.90(1H, d, J=16.4Hz), 7.14(1H,s), 7.34(2H, s), 7.52(1H, m), 8.29-8.43(2H, m), 9.25(1H, s).	197-198
6	O	C=O		Ethyl	CH_3	CH_3	0.95(3H, t, J=7.1Hz), 2.05(1H, m), 2.20-2.40(7H, m), 4.81(1H, d, J=16.4Hz), 5.14(1H, d, J=16.4Hz), 7.01-7.52(6H, m), 8.40(1H, m), 9.11(1H, s).	235-236
7	O	C=O		Isopropyl	CH_3	F	1.14(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.22-2.38(4H, m), 4.63(1H, d, J=16.3Hz), 4.94(1H, d, J=16.3Hz), 7.00-7.36(5H, m), 8.41-8.45(2H, m). 9.56(1H, s).	207-209
8	O	C=O		Isopropyl	CH_3	F	1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.27(1H, m), 2.34(3H, s), 4.64(1H, d, J=15.6Hz), 5.00(1H, d, J=16.4Hz), 7.10-7.53(5H, m), 8.27-8.42(2H, m), 9.41(1H, s).	211-212
9	O	C=O		Isopropyl	CH_3	F	1.13(3H, d, J=6.9Hz), 1.22(3H, d, J=6.9Hz), 2.20-2.35(4H, m), 4.69(1H, d, J=16.4Hz), 5.29(1H, d, J=16.4Hz), 7.00-7.52(6H, m), 8.37(1H, m), 9.15(1H, s).	187-189
10	O	C=O		Ethyl	CH_3	F	0.98(3H, t, J=7.3Hz), 2.05(1H, m), 2.20-2.37(7H, m), 4.70(1H, d, J=16.4Hz), 4.92(1H, d, J=16.4Hz), 7.00-7.37(5H, m), 8.44-8.46(2H, m), 10.39(1H, s).	233-234
11	O	C=O		Ethyl	CH_3	F	0.95(3H, t, J=7.3Hz), 2.02(1H, m), 2.05(1H, m), 2.33(3H, s), 4.72(1H, d, J=16.4Hz), 5.02(1H, d, J=16.4Hz), 7.11-7.56(5H, m), 8.30-8.44(2H, m).	189-190
12	O	C=O		Ethyl	CH_3	F	0.96(3H, t, J=7.3Hz), 2.03(1H, m), 2.22(1H, m), 2.33(3H, s), 4.74(1H, d, J=16.4Hz), 5.23(1H, d, J=16.4Hz), 7.02-7.53(6H, m), 8.39(1H, m), 9.17(1H, s).	158-159

Table 3 (Continued)

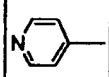
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
13	O	C=O		Isopropyl	F	F	1.15(3H, d, J=7.0Hz), 1.23(3H, d, J=7.0Hz), 2.26(1H, m), 4.63(1H, d, J=16.2Hz), 4.94(1H, d, J=16.2Hz), 6.97-7.26(5H, m), 8.43-8.46(2H, m), 8.90(1H, s).	189-190
14	O	C=O		Isopropyl	F	F	1.12(3H, d, J=6.7Hz), 1.21(3H, d, J=6.7Hz), 2.23(1H, m), 4.63(1H, d, J=15.8Hz), 5.06(1H, d, J=15.8Hz), 7.01-7.54(5H, m), 8.26(1H, m), 8.42(1H, m), 9.49(1H, s).	227-230
15	O	C=O		Isopropyl	F	F	1.15(3H, d, J=6.9Hz), 1.22(3H, d, J=6.9Hz), 2.23(1H, m), 4.62(1H, d, J=16.6Hz), 5.31(1H, d, J=16.6Hz), 6.95-7.54(6H, m), 8.37(1H, m), 9.10(1H, s).	214-215
16	O	C=O		Ethyl	F	F	0.97(3H, t, J=7.4Hz), 2.02(1H, m), 2.25(1H, m), 4.65-4.92(2H, m), 6.99-7.40(5H, m), 8.43-8.46(2H, m), 9.73(1H, s).	223-224
17	O	C=O		Ethyl	F	F	0.96(3H, t, J=7.3Hz), 2.00(1H, m), 2.22(1H, m), 4.68(1H, m), 5.04(1H, m), 7.03-7.27(4H, m), 7.54(1H, m), 8.28-8.44(2H, m), 9.89(1H, s).	217-218
18	O	C=O		Ethyl	F	F	0.97(3H, t, J=7.5Hz), 2.01(1H, m), 2.22(1H, m), 4.76(1H, m), 5.31(1H, m), 6.95-7.55(6H, m), 8.37(1H, m), 9.03(1H, s).	206-207
19	O	C=O		Isopropyl	Cl	Cl	1.12(3H, d, J=6.9Hz), 1.25(3H, d, J=6.9Hz), 2.21(1H, m), 4.59(1H, d, J=16.6Hz), 4.99(1H, d, J=16.6Hz), 6.98(2H, d, J=5.9Hz), 7.55(3H, s), 8.44(2H, d, J=5.9Hz).	232-233
20	O	C=O		Ethyl	Cl	Cl	0.98(3H, t, J=7.5Hz), 2.05(1H, m), 2.28(1H, m), 4.68(1H, d, J=16.5Hz), 5.02(1H, d, J=16.5Hz), 6.98(2H, d, J=5.9Hz), 7.54-7.74(3H, m), 8.45(2H, d, J=5.9Hz), 9.36(1H, s).	243-245

Table 3 (Continued)

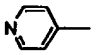
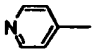
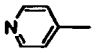
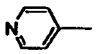
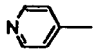
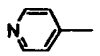
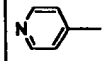
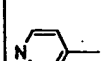
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
21	O	C=O		Isopropyl	CH_3	Cl	1.14(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.20-2.38(4H, m), 4.61(1H, d, J=16.3Hz), 4.95(1H, d, J=16.3Hz), 6.97-8.44(7H, m), 9.35(1H, s).	248-249
22	O	C=O		Isopropyl	CH_2F	CH_3	1.07(3H, d, J=6.7Hz), 1.18(3H, d, J=6.7Hz), 2.25(1H, m), 2.32(3H, s), 4.61(1H, d, J=16.4Hz), 4.84(1H, d, J=16.4Hz), 5.29(2H, d, J=47.2Hz), 6.97(2H, d, J=5.9Hz), 7.39-7.53(3H, m), 8.32(2H, d, J=5.9Hz).	190 (dec.)
23	O	C=O		Ethyl	CH_2F	CH_3	0.97(3H, t, J=7.5Hz), 2.04(1H, m), 2.25(1H, m), 2.36(3H, s), 4.68(1H, d, J=15.0Hz), 4.94(1H, d, J=15.0Hz), 5.33(2H, d, J=47.2Hz), 6.98-7.01(2H, m), 7.42-7.54(3H, m), 8.39-8.42(2H, m), 9.48(1H, s).	227-228
24	O	O		Isopropyl	CH_3	CH_3	1.14(6H, d, J=7.1Hz), 2.27(6H, s), 2.84(1H, m), 4.88(2H, s), 6.44(2H, s), 6.75(1H, s), 7.11(2H, dd, J=4.5Hz, J=1.6Hz), 8.54(2H, dd, J=4.5Hz, J=1.6Hz), 9.79(1H, s).	213-215
25	O	O		Ethyl	CH_3	CH_3	0.94(3H, t, J=7.5Hz), 2.21(2H, q, J=7.5Hz), 2.27(6H, s), 4.92(2H, s), 6.45(2H, s), 6.76(1H, s), 7.13(2H, d, J=6.1Hz), 8.54(2H, d, J=6.1Hz), 8.95(1H, s).	229-230
26	O	S		Isopropyl	Cl	Cl	1.21(6H, d, J=6.9Hz), 3.33(1H, m), 5.20(2H, s), 6.81-7.11(5H, m), 8.43-8.46(2H, m), 9.70(1H, s).	198-199
27	O	S		Isopropyl	CH_3	CH_3	1.26(6H, d, J=6.9Hz), 2.21(6H, s), 3.52(1H, m), 5.25(2H, s), 6.65(2H, s), 6.80(1H, s), 7.01(2H, d, J=5.7Hz), 8.50(2H, d, J=5.7Hz), 10.82(1H, s).	186-187
28	O	S		Ethyl	CH_3	CH_3	1.07(3H, t, J=7.5Hz), 2.23(6H, s), 2.73(2H, q, J=7.5Hz), 5.21(2H, s), 6.68(2H, s), 6.82(1H, s), 6.98(2H, d, J=6.3Hz), 8.48(2H, d, J=6.3Hz), 8.97(1H, s).	191-192

Table 3 (Continued)

Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
29	O	C=O		Isopropyl	CF_3	CF_3	1.14(3H, d, J=6.9Hz), 1.24(3H, d, J=6.9Hz), 2.18(1H, m), 4.51(1H, d, J=16.3Hz), 5.28(1H, d, J=16.3Hz), 6.95(2H, d, J=6.1Hz), 8.07(1H, s), 8.11(2H, s), 8.37(2H, d, J=6.1Hz).	236-237
30	O	C=O		Ethyl	CF_3	CF_3	0.97(3H, t, J=7.3Hz), 2.00-2.35(2H, m), 4.60(1H, m), 5.22(1H, m), 6.94-6.98(2H, m), 8.07(3H, s), 8.35-8.38(2H, m), 9.73(1H, s).	208-209
31	O	C=O		Isopropyl	CF_3	CF_3	1.14(3H, t, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.16(1H, m), 4.51(1H, d, J=16.4Hz), 5.51(1H, d, J=16.4Hz), 6.94-7.49(3H, m), 8.03-8.32(4H, m), 9.61(1H, s).	185-186
32	O	C=O		Isopropyl	CH_3	H	1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.26-2.36(4H, m), 4.65(1H, d, J=16.0Hz), 4.86(1H, d, J=16.0Hz), 6.97(2H, d, J=5.9Hz), 7.25-7.60(4H, m), 8.38(2H, d, J=5.9Hz).	226-227
33	O	C=O		Ethyl	CH_3	H	0.97(3H, t, J=7.4Hz), 2.06(1H, m), 2.26(1H, m), 2.34(3H, s), 4.72(1H, d, J=16.0Hz), 4.84(1H, d, J=16.0Hz), 6.99-7.02(2H, m), 7.29-7.62(4H, m), 8.41-8.44(2H, m), 9.93(1H, s).	218-219
34	O	C=O		Isopropyl	H	H	1.15(3H, d, J=6.9Hz), 1.25(3H, d, J=6.9Hz), 2.34(1H, m), 4.70(1H, d, J=16.4Hz), 4.87(1H, d, J=16.4Hz), 6.99-7.82(7H, m), 8.40-8.44(2H, m), 10.16(1H, s).	238-239
35	O	C=O		Ethyl	H	H	0.97(3H, t, J=7.4Hz), 2.05(1H, m), 2.24(1H, m), 4.65-4.94(2H, m), 6.99-7.80(7H, m), 8.40-8.44(2H, m), 9.68(1H, s).	219-220
36	O	C=O		Isopropyl	CH_3	CH_3	1.08(3H, d, J=6.9Hz), 1.21(3H, d, J=6.9Hz), 2.20-2.40(7H, m), 4.59(1H, d, J=15.6Hz), 5.07(1H, d, J=15.6Hz), 7.02-7.12(5H, m), 7.18(1H, s), 7.26(2H, s), 8.85(1H, s).	199-200

Table 3 (Continued)

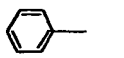
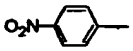
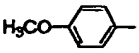
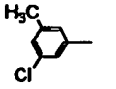
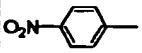
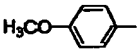
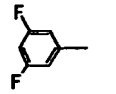
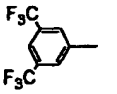
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
37	O	C=O		Ethyl	CH_3	CH_3	0.93(3H, t, J=7.3Hz), 2.02(1H, m), 2.12-2.28(7H, m), 4.64(1H, d, J=15.6Hz), 5.07(1H, d, J=15.6Hz), 7.02-7.26(8H, m), 8.97(1H, s).	221-222
38	O	C=O		Isopropyl	CH_3	CH_3	1.12(3H, d, J=6.9Ha), 1.22(3H, d, J=6.9Hz), 2.20-2.40(7H, m), 4.77(1H, d, J=16.0Hz), 4.98(1H, d, J=16.0Hz), 7.23-7.32(5H, m), 8.00(2H, d, J=8.5Hz), 8.97(1H, s).	203-204
39	O	C=O		Isopropyl	CH_3	CH_3	1.07(3H, d, J=6.9Hz), 1.20(3H, d, J=6.9Hz), 2.20-2.40(7H, m), 3.69(3H, s), 4.50(1H, d, J=15.2Hz), 5.07(1H, d, J=15.2Hz), 6.57-7.31(7H, m), 8.74(1H, s).	156-157
40	O	C=O		Isopropyl	CH_3	CH_3	1.10(3H, d, J=6.7Hz), 1.21(3H, d, J=6.7Hz), 2.11(3H, s), 2.25-2.38(7H, m), 4.34(1H, d, J=15.8Hz), 5.23(1H, d, J=15.8Hz), 6.66(1H, s), 6.77(1H, s), 6.83(1H, s), 7.19(1H, s), 7.27(2H, s), 8.72(1H, s).	226-227
41	O	C=O		Ethyl	CH_3	CH_3	0.96(3H, t, J=7.5Hz), 2.08(1H, m), 2.20-2.40(7H, m), 4.84(1H, d, J=16.6Hz), 5.00(1H, d, J=16.6Hz), 7.25-7.32(5H, m), 7.98-8.05(2H, m), 9.43(1H, s).	230-231
42	O	C=O		Ethyl	CH_3	CH_3	0.92(3H, t, J=7.3Hz), 2.05(1H, m), 2.10-2.40(7H, m), 3.69(3H, s), 4.56(1H, d, J=15.4Hz), 5.07(1H, d, J=15.4Hz), 6.59-7.26(7H, m), 9.25(1H, s).	157-158
43	O	C=O		Isopropyl	CH_3	CH_3	1.12(3H, d, J=6.9Hz), 1.22(3H, d, J=6.9Hz), 2.22-2.40(7H, m), 4.54(1H, d, J=16.3Hz), 4.99(1H, d, J=16.3Hz), 6.50-6.60(3H, m), 7.24(1H, s), 7.35(2H, s), 9.25(1H, s).	208-209
44	O	C=O		Isopropyl	CH_3	CH_3	1.12(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.25(6H, s), 2.30(1H, m), 4.62(1H, d, J=15.9Hz), 5.33(1H, d, J=15.9Hz), 7.19-7.30(3H, m), 7.51(2H, s), 7.58(1H, s), 9.92(1H, s).	184-185

Table 3 (Continued)

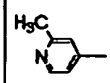
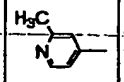
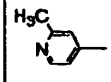
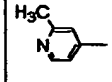
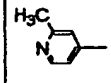
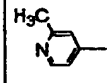
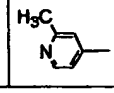
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
45	O	C=O		Isopropyl	CH_3	CH_3	1.05(3H, d, J=6.7Hz), 1.15(3H, d, J=6.7Hz), 2.22-2.32(10H, m), 4.44(1H, d, J=16.0Hz), 4.90(1H, d, J=16.0Hz), 6.69-6.72(2H, m), 7.16(1H, s), 7.19(2H, s), 8.20(1H, d, J=5.5Hz), 8.82(1H, s).	269-270
46	O	C=O		Isopropyl	CH_3	F	1.15(3H, d, J=7.0Hz), 1.20(3H, d, J=7.0Hz), 2.21(1H, m), 2.24(3H, s), 2.34(3H, s), 4.42(1H, d, J=16.2Hz), 4.96(1H, d, J=16.2Hz), 6.70-7.26(5H, m), 8.21(1H, d, J=5.9Hz), 9.25(1H, s).	217-218
47	O	C=O		Isopropyl	CH_3	Cl	1.14(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.22-2.38(4H, m), 2.41(3H, s), 4.46(1H, d, J=16.2Hz), 5.07(1H, d, J=16.2Hz), 6.77-8.30(6H, m), 9.50(1H, s),	253-254
48	O	C=O		Isopropyl	Cl	Cl	1.15(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.23(1H, m), 2.44(3H, s), 4.41(1H, d, J=16.2Hz), 5.18(1H, d, J=16.2Hz), 6.75-8.30(6H, m), 9.42(1H, s).	234-236
49	O	C=O		Isopropyl	CH_2F	CH_3	1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.26-2.37(7H, m), 4.48(1H, d, J=16.5Hz), 5.04(1H, d, J=16.5Hz), 5.31(2H, d, J=47.2Hz), 6.75-6.78(2H, m), 7.39-7.52(3H, m), 8.24(1H, m), 8.85(1H, s).	253-255
50	O	C=O		Isopropyl	CH_3	H	1.13(3H, d, J=7.0Hz), 1.23(3H, d, J=7.0Hz), 2.24-2.39(7H, m), 4.54(1H, d, J=16.1Hz), 4.95(1H, d, J=16.1Hz), 6.77-8.28(7H, m), 8.96(1H, s).	219-220
51	O	C=O		Isopropyl	CH_3	CH_3	1.15(3H, d, J=6.7Hz), 1.24(3H, d, J=6.7Hz), 2.28-2.42(7H, m), 4.55(1H, d, J=16.4Hz), 4.97(1H, d, J=16.4Hz), 6.94-6.96(2H, m), 7.26(1H, s), 7.35(2H, s), 8.18(1H, m), 9.29(1H, s).	253-254
52	O	C=O		Ethyl	CH_3	CH_3	0.96(3H, t, J=7.5Hz), 2.05(1H, m), 2.20-2.30(7H, m), 2.40(3H, s), 4.57(1H, d, J=16.3Hz), 4.96(1H, d, J=16.3Hz), 6.79-6.82(2H, m), 7.24(1H, s), 7.31(2H, s), 8.29(1H, d, J=4.6Hz), 9.55(1H, s).	211-212

Table 3 (Continued)

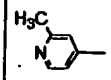
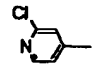
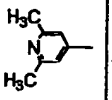
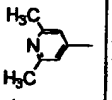
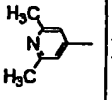
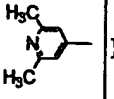
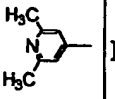
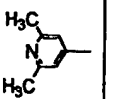
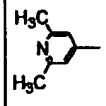
Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
53	O	C=O		Ethyl	CH_3	F	0.97(3H, t, J=7.4Hz), 2.02(1H, m), 2.22-2.31(4H, m), 2.42(3H, s), 4.56(1H, d, J=16.8Hz), 5.02(1H, d, J=16.8Hz), 6.79-7.33(5H, m), 8.30(1H, m), 9.64(1H, s).	183-184
54	O	C=O		Ethyl	CH_3	CH_3	0.98(3H, t, J=7.5Hz), 2.10(1H, m), 2.25-2.32(7H, m), 4.59(1H, d, J=15.6Hz), 4.96(1H, d, J=15.6Hz), 6.94-6.97(2H, m), 7.27(1H, s), 7.33(2H, s), 8.19(1H, m), 9.34(1H, s).	217-218
55	O	C=O		Isopropyl	CH_3	CH_3	1.11(3H, d, J=6.7Hz), 1.21(3H, d, J=6.7Hz), 2.22-2.38(13H, m), 4.37(1H, d, J=16.0Hz), 5.05(1H, d, J=16.0Hz), 6.56(2H, s), 7.19(1H, s), 7.27(2H, s), 9.70(1H, s).	232-233
56	O	C=O		Isopropyl	F	F	1.15(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.23(1H, m), 2.36(6H, s), 4.34(1H, d, J=16.2Hz), 5.18(1H, d, J=16.2Hz), 6.58(2H, s), 7.01-7.20(3H, m), 9.25(1H, s).	176-178
57	O	C=O		Isopropyl	Cl	Cl	1.13(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.20(1H, m), 2.35(6H, s), 4.22(1H, d, J=16.3Hz), 5.30(1H, d, J=16.3Hz), 6.54(2H, s), 7.46(2H, s), 7.50(1H, s), 9.35(1H, s).	172-173 (foam)
58	O	C=O		Isopropyl	CH_2F	CH_3	1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.22-2.35(10H, m), 4.35(1H, d, J=16.0Hz), 5.13(1H, d, J=16.0Hz), 5.31(2H, d, J=47.2Hz), 6.56(2H, s), 7.37-7.50(3H, m), 9.06(1H, s).	197-198 (foam)
59	O	C=O		Isopropyl	Cl	CH_3	1.13(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.20-2.35(10H, m), 4.32(1H, d, J=16.0Hz), 5.19(1H, d, J=16.0Hz), 6.56(2H, s), 7.27-7.50(3H, m), 9.34(1H. s).	222-223
60	O	C=O		Ethyl	CH_3	CH_3	0.95(3H, t, J=7.5Hz), 2.02(1H, m), 2.20-2.33(13H, m), 4.45(1H, d, J=16.0Hz), 5.05(1H, d, J=16.0Hz), 6.59(2H, s), 7.22(1H, s), 7.29(2H, s), 9.45(1H, s).	211-212

Table 3 (Continued)

Ex. No.	A	Z	R^1	R^2	R^3	R^4	^{1}H-NMR(200MHz, $CDCl_3$) δ	M.p.(℃)
61	O	C=O		Ethyl	F	F	1.15(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.23(1H, m), 2.36(6H, s), 4.34(1H, d, J=16.2Hz), 5.18(1H, d, J=16.2Hz), 6.58(2H, s), 7.01-7.20(3H, m), 9.25(1H, s).	176-178
62	O	C=O		Isopropyl	CH_3	CH_3	1.14(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.30-2.40(7H, m), 4.69(1H, d, J=16.4Hz), 4.86(1H, d, J=16.4Hz), 7.27-7.37(5H, m), 8.52(1H, m), 9.50(1H, s).	236-238
63	O	C=O		Isopropyl	CH_3	Cl	1.16(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.30(1H, m), 2.40(3H, s), 4.77(2H, s), 7.27-7.56(5H, m), 8.56(1H, d, J=5.1Hz), 9.27(1H, s).	220-221
64	O	C=O		Isopropyl	CH_3	NO_2	($CDCl_3$/CD_3OD) δ 1.11(3H, d, J=7.1Hz), 1.23(3H, d, J=7.1Hz), 2.23(1H, m), 2.49(3H, s), 4.63(1H, d, J=16.2Hz), 4.98(1H, d, J=16.2Hz), 7.02(2H, d, J=5.7Hz), 7.84(1H, s), 8.27-8.35(4H, m).	256-257
65	O	C=O		Isopropyl	CH_3	NO_2	1.13(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.22(1H, m), 2.37(3H, s), 2.46(3H, s), 4.41(1H, d, J=16.2Hz), 5.25(1H, d, J=16.2Hz), 6.75-6.79(2H, m), 7.76(1H, s), 8.21-8.28(3H, m), 9.76(1H, s).	237-238

Example 66 : Synthesis of 1-(4'-picolyl)-5-isopropyl-6-(3',5'-dimethylphenylamino)-2,4-pyrimidinedione (Compound 66)

To a magnetically stirred DMF solution (10ml) of compound (II-a-1) obtained in Preparation 22 (630mg, 2mmol) at room temperature, were added anhydrous potassium carbonate (552mg, 4mmol), lithium iodide (268mg, 2mmol), and 4-picolyl chloride hydrochloride (328mg, 2mmol). After stirring for 24hr, the solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - ethyl acetate) to give 276mg (yield 34%) of 1-(4'-picolyl)-5-isopropyl-6-(3',5'-dimethylphenylacetamido)-2,4-pyrimidinedione. The compound thus obtained was then refluxed in methanol (10ml) with sodium methoxide (110mg, 2mmol) for 6hr. The reaction mixture was allowed to cool to room temperature and neutralized with excess ammonium chloride. The solvent was removed under reduced pressure and the resulting residue was purified by flash chromatography (eluent - methanol:ether=8:92) to afford 280mg (yield 88%) of the title compound as a white solid.

M.p. : 272 to 273 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.20(6H, d, J=6.9Hz), 2.24(6H, s), 2.90(1H, m), 4.90(2H, s), 6.27(2H, s), 6.61(1H, s), 7.04-7.06(2H, m), 8.42-8.45(2H, m)

m/z(EI) 364(M^+).

Example 67 : Synthesis of 1-(4'-picolyl)-5-ethyl-6-(3',5'-dimethylphenylamino)-2,4-pyrimidinedione (Compound 67)

The procedure of Example 66 was repeated using compound (II-a-2) obtained in Preparation 23 in place of compound (II-a-1) to prepare the title compound.

M.p. : 250 to 251 °C

^{1}H-NMR(200MHz, $CDCl_3/CD_3OD$) δ 0.99(3H, t, J=7.5Hz), 2.24(6H, s), 2.37(2H, q, J=7.5Hz), 4.91(2H, s), 6.31(2H, s), 6.62(1H,

s), 7.04-7.07(2H, m), 8.40-8.43(2H, m)
m/z(EI) 350(M^+).

Example 68 : Synthesis of 1-(N-oxo-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 68)

Compound 1 obtained in Example 1 (2.26g, 6mmol) was stirred with m-chloroperbenzoic acid (2.72g, 9mmol) in dichloromethane (120ml) at room temperature. After 6hr, the solvent was removed and the residue was purified by flash chromatography (eluent - chloroform:methanol=93:7) to afford 2g (yield 84%) of the title compound as a white solid.
M.p. : 254 to 255 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.25-2.36(7H, m), 4.69(2H, s), 7.05-7.41(5H, m), 8.05-8.09(2H, m), 9.52(1H, s)
m/z(EI) 393(M^+).

Example 69 : Synthesis of 1-(N-oxo-3'-methyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 69)

Compound 45 obtained in Example 45 (834mg, 2.13mmol) was stirred with m-chloroperbenzoic acid (969mg, 3.2mmol) in dichloromethane (40ml) at room temperature. After 5hr, the solvent was removed and the residue was purified by flash chromatography (eluent - ethyl acetate:methanol=7:1) to afford 860mg (yield 99%) of the title compound as a white solid.
M.p. : 223 to 224 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.13(3H, d, J=6.7Hz), 1.23(3H, d, J=6.7Hz), 2.25-2.40(10H, m), 4.56(1H, d, J=16.0Hz), 4.85(1H, d, J=16.0Hz), 6.93(1H, m), 7.31(1H, s), 7.37(2H, s), 8.10(1H, m), 10.08(1H, s)
m/z(EI) 407(M^+).

Example 70 : Synthesis of 1-(N-oxo-3',5'-dimethyl-4'-

picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 70)

Compound 55 obtained in Example 55 (840mg, 2mmol) was stirred with m-chloroperbenzoic acid (942mg, 3mmol) in dichloromethane (40ml) at room temperature. After 21hr, the solvent was removed and the residue was purified by flash chromatography (eluent - dichloromethane:methanol=15:1) to afford 800mg (yield 95%) of the title compound as a white solid.

M.p. : 241 to 242 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.12(3H, d, J=6.7Hz), 1.22(3H, d, J=6.7Hz), 2.30-2.34(13H, m), 4.41(1H, d, J=16.0Hz), 4.98(1H, d, J=16.0Hz), 6.80(2H, s), 7.27(1H, s), 7.34(2H, s), 9.21(1H, s)

m/z(EI) 421(M^+).

Example 71 : Synthesis of 1-(N-oxo-3',5'-dimethyl-4'-picolyl)-5-isopropyl-6-(3'-chloro-5'-methylbenzoyl)-2,4-pyrimidinedione (Compound 71)

Compound 59 obtained in Example 59 (860mg, 2mmol) was stirred with m-chloroperbenzoic acid (942mg, 3mmol) in dichloromethane (40ml) at room temperature. After 20hr, the solvent was removed and the residue was purified by flash chromatography (eluent - ethyl acetate:hexane=10:1) to afford 870mg (yield 98%) of the title compound as a white solid.

M.p. : 225 to 226 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.13(3H, d, J=6.9Hz), 1.22(3H, d, J=6.9Hz), 2.22-2.36(10H, m), 4.39(1H, d, J=16.0Hz), 5.04(1H, d, J=16.0Hz), 6.80(2H, s), 7.33-7.54(3H, m), 9.14(1H, s)

m/z(EI) 441(M^+).

Example 72 : Synthesis of 1-(3'-acetoxymethyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione

(Compound 72)

Compound 69 obtained in Example 69 (800mg, 1.96mmol) was dissolved in acetic anhydride (10ml) and the solution was heated in an oil bath (120-140 °C) with stirring for 4hr. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (eluent - ethyl acetate:hexane=2:1) to afford 150mg (yield 17%) of the title compound as a syrup.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.14(3H, d, J=6.7Hz), 1.28(3H, d, J=6.7Hz), 2.16(3H, s), 2.22-2.40(7H, m), 4.68(1H, d, J=16.2Hz), 4.88(1H, d, J=16.2Hz), 5.08(2H, s), 7.00-7.02(2H, m), 7.26(1H, s), 7.36(2H, s), 8.44(1H, m)

m/z(EI) 449(M^+).

Example 73 : Synthesis of 1-(3'-acetoxymethyl-5'-methyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 73)

Compound 70 obtained in Example 70 (300mg, 0.71mmol) was dissolved in acetic anhydride (3ml) and the solution was heated in an oil bath (120-130 °C) with stirring for 2hr. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (eluent - ethyl acetate:hexane=1:1) to afford 110mg (yield 33%) of the title compound as a foam.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.13(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.10-2.41(10H, m), 4.53(1H, d, J=16.0Hz), 4.96(1H, d, J=16.0Hz), 5.00(2H, s), 6.78-6.81(2H, m), 7.24(1H, s), 7.34(2H, s)

m/z(EI) 463(M^+).

Example 74 : Synthesis of 1-(3'-acetoxymethyl-5'-methyl-4'-picolyl)-5-isopropyl-6-(3'-chloro-5'-methylbenzoyl)-2,4-pyrimidinedione (Compound 74)

Compound 71 obtained in Example 71 (700mg, 1.58mmol)

was dissolved in acetic anhydride (10ml) and the solution was heated in an oil bath (120-130 °C) with stirring for 5hr. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography (eluent - ethyl acetate:hexane=2:1) to afford 115mg (yield 15%) of the title compound as a foam.

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.14(3H, d, J=6.9Hz), 1.24(3H, d, J=6.9Hz), 2.16(3H, s), 2.20-2.32(4H, m), 2.42(3H, s), 4.48(1H, d, J=16.3Hz), 5.00(2H, s), 5.06(1H, d, J=16.3Hz), 6.76(2H, d, J=5.9Hz), 7.32(1H, s), 7.39(1H, s), 7.52(1H, s), 9.46(1H, s)

m/z(EI) 483(M^+).

Example 75 : Synthesis of 1-(3'-hydroxymethyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 75)

Compound 72 obtained in Example 72 (100mg, 0.22mmol) was stirred with ammonium hydroxide (0.5ml) in methanol (5ml) at room temperature. After 6hr, the solvent was evaporated in vacuo and the resulting residue was recrystallized from methanol-chloroform to give 70mg (yield 77%) of the title compound as a white solid.

M.p. : 256 to 257 °C

^{1}H-NMR(200MHz, DMSO-d_6) δ 1.05(3H, d, J=6.8Hz), 1.11(3H, d, J=6.8Hz), 2.15(1H, m), 2.28(6H, s), 4.44(2H, d, J=5.5Hz), 4.59(1H, d, J=16.7Hz), 4.70(1H, d, J=16.7Hz), 5.35(1H, t, J=5.5Hz), 6.90(1H, m), 7.15(1H, s), 7.32(1H, s), 7.55(2H, s), 8.25(1H, m), 11.66(1H, s)

m/z(EI) 407(M^+).

Example 76 : Synthesis of 1-(3'-hydroxymethyl-5'-methyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 76)

Compound 73 obtained in Example 73 (150mg, 0.32mmol) was stirred with ammonium hydroxide (0.5ml) in methanol

(5ml) at room temperature. After 5hr, the solvent was evaporated in vacuo and the resulting residue was recrystallized from methanol-chloroform to give 100mg (yield 74%) of the title compound as a white solid.

M.p. : 234 to 236 °C

^{1}H-NMR(200MHz, DMSO-d_6) δ 1.05(3H, d, J=6.7Hz), 1.11(3H, d, J=6.7Hz), 2.15(1H, m), 2.26(9H, s), 4.37(2H, d, J=5.3Hz), 4.51(1H, d, J=17.1Hz), 4.72(1H, d, J=17.1Hz), 5.29(1H, t, J=5.3Hz), 6.72(1H, s), 6.93(1H, s), 7.30(1H, s), 7.51(2H, s), 11.64(1H, s)

m/z(EI) 421(M^+).

Example 77 : Synthesis of 1-(3'-hydroxymethyl-5'-methyl-4'-picolyl)-5-isopropyl-6-(3'-chloro-5'-methylbenzoyl)-2,4-pyrimidinedione (Compound 77)

Compound 74 obtained in Example 74 (100mg, 0.21mmol) was stirred with ammonium hydroxide (0.5ml) in methanol (5ml) at room temperature. After 6hr, the solvent was evaporated in vacuo and the resulting residue was recrystallized from methanol-chloroform to afford 78mg (yield 85%) of the title compound as a white solid.

M.p. : 238 to 240 °C

^{1}H-NMR(200MHz, DMSO-d_6) δ 1.05(3H, d, J=6.8Hz), 1.10(3H, d, J=6.8Hz), 2.11(1H, m), 2.27(3H, s), 2.49(3H, s), 4.37(2H, d, J=5.7Hz), 4.47(1H, d, J=17.1Hz), 4.82(1H, d, J=17.1Hz), 5.27(1H, t, J=5.7Hz), 6.75(1H, s), 6.93(1H, s), 7.56(1H, s), 7.66(1H, s), 7.74(1H, s), 11.63(1H, s)

m/z(EI) 441(M^+).

Example 78 : Synthesis of 1-(3'-methoxycarbonyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 78)

Compound 62 obtained in Example 62 (100mg, 0.25mmol) was stirred with potassium carbonate (138mg, 1mmol) and distilled water (0.5ml) in methanol (5ml) at room

temperature. After 18hr, the reaction mixture was acidified with glacial acetic acid and the solvent was evaporated in vacuo. The resulting residue was purified by flash chromatography (eluent - ethyl acetate:hexane=4:1) to afford 74mg (yield 68%) of the title compound as a white solid.
M.p. : 138 to 140 °C
^{1}H-NMR(200MHz, $CDCl_3$) δ 1.14(3H, d, J=6.9Hz), 1.23(3H, d, J=6.9Hz), 2.28-2.38(7H, m), 3.98(3H, s), 4.68(1H, d, J=16.0Hz), 5.00(1H, d, J=16.0Hz), 7.21-7.33(4H, m), 7.73(1H, s), 8.54(1H, m), 9.45(1H, s)
m/z(EI) 435(M^+).

Example 79 : Synthesis of 1-(3'-carbamoyl-4'-picolyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 79)

Compound 62 obtained in Example 62 (60mg, 0.15mmol) was stirred with conc. sulfuric acid (1ml) in an oil bath (80 °C). After 10min, the reaction mixture was allowed to cool to room temperature and poured into distilled water (10ml). The resulting precipitate was collected by filtration, washed with distilled water and hexane, and dried in vacuo to afford 38mg (yield 61%) of the title compound as a white solid.
M.p. : 295 to 296 °C
^{1}H-NMR(500MHz, DMSO-d_6) δ 1.03(3H, d, J=6.9Hz), 1.10(3H, d, J=6.9Hz), 2.14(1H, m), 2.25(6H, s), 4.67(1H, d, J=17.6Hz), 4.75(1H, d, J=17.6Hz), 7.26(1H, dd, J=5.0Hz, J=1.7Hz), 7.29(1H, s), 7.53(2H, s), 7.63(1H, d, J=2.5Hz), 7.69(1H, s), 8.04(1H, d, J=2.1Hz), 8.40(1H, d, J=5.0Hz), 11.71(1H, s)
m/z(EI) 420(M^+).

Example 80 : Synthesis of 1-(3'-carbamoyl-4'-picolyl)-5-isopropyl-6-(3'-chloro-5'-methylbenzoyl)-2,4-pyrimidinedione (Compound 80)

Compound 63 obtained in Example 63 (90mg, 0.21mmol) was

stirred with conc. sulfuric acid (1ml) in an oil bath (80 °C). After 10min, the reaction mixture was allowed to cool to room temperature and poured into distilled water (10ml). The resulting precipitate was collected by filtration, washed with distilled water and hexane, and dried in vacuo to afford 87mg (yield 92%) of the title compound as a white solid.

M.p. : 284 to 285 °C

^{1}H-NMR(500MHz, DMSO-d_6) δ 1.03(3H, d, J=6.8Hz), 1.10(3H, d, J=6.8Hz), 2.12(1H, m), 2.29(3H, s), 4.68(1H, d, J=17.3Hz), 4.76(1H, d, J=17.3Hz), 7.29(1H, dd, J=5.0Hz, J=1.7Hz), 7.58(1H, s), 7.63(1H, d, J=2.5Hz), 7.71(1H, s), 7.74(1H, s), 7.80(1H, s), 8.04(1H, d, J=2.5Hz), 8.41(1H, d, J=5.0Hz), 11.72(1H, s)

m/z(EI) 440(M^+).

Example 81 : Synthesis of 1-(4'-aminobenzyl)-5-isopropyl-6-(3',5'-dimethylbenzoyl)-2,4-pyrimidinedione (Compound 81)

Compound 38 obtained in Example 38 (50mg, 0.12mmol) in methanol (5ml) was stirred under an atmosphere of hydrogen in the presence of platinium oxide catalyst (10mg) at room temperature for 4hr. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography (eluent - ethyl acetate:hexane=1:1) to afford 32mg (yield 70%) of the title compound as a yellow solid.

M.p. : 173 to 175 °C

^{1}H-NMR(200MHz, $CDCl_3$) δ 1.07(3H, d, J=6.9Hz), 1.20(3H, d, J=6.9Hz), 2.20-2.40(7H, m), 3.57(2H, s), 4.46(1H, d, J=15.2Hz), 5.00(1H, d, J=15.2Hz), 6.35(2H, d, J=8.3Hz), 6.81(2H, d, J=8.3Hz), 7.21(1H, s), 7.26(2H, s), 8.86(1H, s)

m/z(EI) 391(M^+).

Antiviral Activity and Cytotoxicity Test

The in vitro anti-HIV-1 assays were based on the inhibition of the virus-induced cytopathic effect in MT-4 cells, as described in J. Med. Chem, 34, 349 (1991).

First, MT-4 cells were suspended in a culture medium at a concentration of 1 x 10^4 cells/ml and infected with 500 $TCID_{50}$ (50% cell culture infective dose)/well of HIV-1. Immediately after the virus infection, 100 μl of the cell suspension was added to each of the wells of a flat-bottomed microtiter tray containing various concentrations of the test compounds(1) to (81). After incubating for 4 or 5 days at 37 °C, the number of viable cells was determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method, as disclosed in J. Virol. Methods, 20, 309 (1988).

The cytotoxicity of the compounds of the present invention was assessed in parallel with their antiviral activity. It was based on the viability of mock-infected host cells as determined by the MTT method (see J. Virol. Methods, 20, 309 (1988)). MKC-442(6-benzyl-1-ethoxymethyl-5-isopropyluracil) was employed as a comparative compound.

The results of the tests are shown in Table 4.

Table 4

Ex. No. (Compound)	CD_{50}(μg/mℓ)*	ED_{50}(μg/mℓ)**	S.I. (CD_{50}/ED_{50})***
1	22.6	0.0026	8,600
2	27.2	0.0036	7,578
3	26.1	0.0055	4,788
4	64.0	0.0027	23,940
5	18.7	0.012	1,553
6	28.2	0.0127	2,215
7	22.7	0.0034	6,597
8	28.16	0.008	3,451
9	40.5	0.0119	3,401
10	51.7	0.0101	5,133
11	47.4	0.0178	2,658
12	38.9	0.0542	716
13	42.3	0.0124	3,414
14	29.81	0.049	612
15	49.87	0.053	943
16	50.6	0.0601	841
17	74.3	0.112	663
18	93.2	0.1189	784
19	11.28	0.003	3,394
20	32.9	0.012	2,758
21	55.07	0.0023	23,501
22	92.8	0.002	48,305
MKC-442	27.7	0.005	5,544

Foot note:

* CD_{50}: Cytotoxic concentration that causes death of MT-4 cells by 50 %

** ED_{50}: Effective concentration for the inhibition of the proliferation of HIV-1 by 50%

*** S.I.: Selectivity index = (CD_{50}/ED_{50})

Table 4 (Continued)

Ex. No. (Compound)	CD_{50}(μg/mℓ)*	ED_{50}(μg/mℓ)**	S.I. (CD_{50}/ED_{50})***
23	52.1	0.003	15,245
24	15.8	0.010	1,628
25	>100	0.018	>5,557
26	6.5	0.003	2,112
27	8.5	0.002	5,747
28	12.5	0.004	3,516
29	44.9	1.867	24
30	52.3	1.935	27
31	11.7	1.8	6
32	40.4	0.003	12,039
33	57.1	0.011	5,073
34	37.4	0.014	2,663
35	>100	0.0606	>1,650
36	8.01	0.004	2,170
37	5.78	0.003	2,066
38	5.65	0.005	1,172
39	7.46	0.003	2,654
40	7.97	0.0348	229
41	4.63	0.009	497
42	2.14	0.002	921
43	7.16	0.0035	2,057
44	8.17	1.80	5
MKC-442	27.7	0.005	5,544

Foot note:

* CD_{50}: Cytotoxic concentration that causes death of MT-4 cells by 50 %

** ED_{50}: Effective concentration for the inhibition of the proliferation of HIV-1 by 50%

*** S.I.: Selectivity index = (CD_{50}/ED_{50})

Table 4 (Continued)

Ex. No. (Compound)	CD_{50}(μg/mℓ)*	ED_{50}(μg/mℓ)**	S.I. (CD_{50}/ED_{50})***
45	>100	0.0098	>10,170
46	22.9	0.0024	9,691
47	93.75	0.0027	35,133
48	12.07	0.0030	4,021
49	64.39	0.0076	8,440
50	47.68	0.0029	16,351
51	17.1	0.0010	17,812
52	14.3	0.0010	14,684
53	37.8	0.0031	12,110
54	8.7	0.0017	4,992
55	9.9	0.0010	10,274
56	87.2	0.0044	19,648
57	9.46	0.0028	3,411
58	36.03	0.0025	14,300
59	8.68	0.0021	4,126
60	17.5	0.0026	6,739
61	37.5	0.0151	2,475
62	9.15	0.0016	5,858
63	8.55	0.0029	2,966
64	46	0.0096	4,801
65	44.08	0.0075	5,916
66	>100	0.08	>1,287
MKC-442	27.7	0.005	5,544

Foot note:

* CD_{50}: Cytotoxic concentration that causes death of MT-4 cells by 50 %

** ED_{50}: Effective concentration for the inhibition of the proliferation of HIV-1 by 50%

*** S.I.: Selectivity index = (CD_{50}/ED_{50})

Table 4 (Continued)

Ex. No. (Compound)	CD_{50}(μg/mℓ)*	ED_{50}(μg/mℓ)**	S.I. (CD_{50}/ED_{50})***
67	54.5	0.42	130
68	56.9	0.0145	3,928
69	48.25	0.0125	3,853
70	25.84	0.0055	4,712
71	25.44	0.0082	3,092
72	38.49	0.0088	4,365
73	39.65	0.0067	5,903
74	28.81	0.0134	2,152
75	42.06	0.0031	13,444
76	38.39	0.0084	4,561
77	23.51	0.0115	2,052
78	40.79	0.0075	5,414
79	>100	0.0091	>10,942
80	27.83	0.0111	2,507
81	9.63	0.015	648
MKC-442	27.7	0.005	5,544

Foot note:

* CD_{50}: Cytotoxic concentration that causes death of MT-4 cells by 50 %

** ED_{50}: Effective concentration for the inhibition of the proliferation of HIV-1 by 50%

*** S.I.: Selectivity index = (CD_{50}/ED_{50})

Antiviral activity against mutant HIV-1

Antiviral activities of the inventive compounds were determined against Y181C which is representative HIV-1 mutant having high resistance against anti-HIV-1 nonnucleosides, e.g., Nevirapine, by the MTT method. MKC-442 was employed as a comparative compound.

The representative results of the tests are shown in Table 5.

Table 5

Compound	EC_{50} (μM)*
1	0.005 - 0.014
4	0.010 - 0.041
MKC-442	13.4**

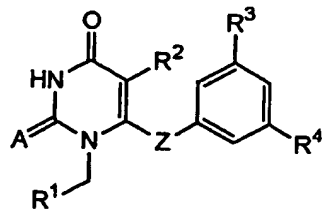
Foot note:
* EC_{50}: Effective concentration for the inhibition of the proliferation of mutant HIV-1 by 50%
** Reference : J. Med. Chem., 42, 4500 (1999)

As the above results show, the novel antiviral 2,4-pyrimidinedione derivatives of the present invention possess high antiviral activity against HIV-1, both wild-type and mutant HIV-1, and at the same time show high selectivity indices, i.e., low toxicity. The inventive compounds can therefore be used as a drug for treating AIDS.

While the invention has been described with respect to the specific embodiments, it should be recognized that various modifications and changes may be made by those skilled in the art to the invention which also fall within the scope of the invention as defined by the appended claims.

What is claimed is:

1. A compound of formula(I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 is a C_{6-10} aryl or C_{3-10} heteroaryl group optionally having one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more halogen atoms, C_{3-6} cycloalkyl, cyano, nitro, hydroxy, thiohydroxy, azido, C_{1-6} alkoxy, oximino, C_{1-3} alkyloximino, O-(C_{1-6} alkyl)-substituted oximino, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, hydroxymethyl, azidomethyl, C_{1-6} alkoxymethyl, C_{1-6} acyloxymethyl, carbamoyloxymethyl, aminomethyl, N-(C_{1-3} alkyl)aminomethyl, N,N-di(C_{1-3} alkyl)aminomethyl, carboxy, C_{1-6} alkoxycarbonyl, aziridine, amino, hydroxyethylamino, cyclopropylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, trifluoroacetamido, C_{1-6} acylamido, carbamoyl, hydroxyethylcarbamoyl, cyclopropylcarbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, aminocarbamoyl, dimethylaminocarbamoyl, hydrazino, 1,1-dimethylhydrazino, imidazolyl, triazolyl and tetrazolyl; a tetrahydropyridyl or piperidyl group optionally substituted with a C_{1-6} alkyl or C_{1-6} alkoxycarbonyl group; a tetrahydropyranyl group; or a tetrahydrofuryl group;

R^2 is hydrogen, halogen, nitro, cyano, C_{1-3} alkoxycarbonyl, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl)carbamoyl, C_{1-6} alkyl, C_{3-6}

cycloalkyl or benzyl;

R^3 and R^4 are each independently hydrogen, halogen, hydroxy, cyano, nitro, amino, acetamido, trifluoroacetamido, azido, C_{1-3} alkyl, C_{1-3} alkyl substituted with one or more halogen atoms, C_{1-3} alkoxycarbonyl, carbamoyl, C_{1-3} alkylcarbamoyl, di(C_{1-3} alkyl)carbamoyl or C_{1-3} alkoxy;

A is O or S; and

Z is O, S, C=O, NH or CH_2.

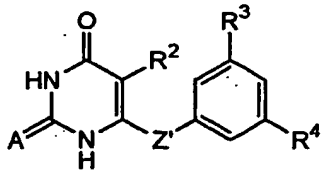
2. The compound of claim 1 wherein R^1 is a phenyl, pyridyl or N-oxopyridyl group optionally having one or more substituents selected from the group consisting of halogen, C_{1-6} alkyl, C_{1-6} alkyl substituted with one or more halogen atoms, C_{3-6} cycloalkyl, cyano, nitro, hydroxy, thiohydroxy, azido, C_{1-6} alkoxy, oximino, C_{1-3} alkyloximino, O-(C_{1-6} alkyl)-substituted oximino, C_{1-6} alkylcarbonyl, C_{3-6} cycloalkylcarbonyl, hydroxymethyl, azidomethyl, C_{1-6} alkoxymethyl, C_{1-6} acyloxymethyl, carbamoyloxymethyl, aminomethyl, N-(C_{1-3} alkyl)aminomethyl, N,N-di(C_{1-3} alkyl)aminomethyl, carboxy, C_{1-6} alkoxycarbonyl, aziridine, amino, hydroxyethylamino, cyclopropylamino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, trifluoroacetamido, C_{1-6} acylamido, carbamoyl, hydroxyethylcarbamoyl, cyclopropylcarbamoyl, C_{1-6} alkylcarbamoyl, di(C_{1-6} alkyl)carbamoyl, aminocarbamoyl, dimethylaminocarbamoyl, hydrazino, 1,1-dimethylhydrazino, imidazolyl, triazolyl and tetrazolyl; a tetrahydropyridyl or piperidyl group optionally substituted with a C_{1-6} alkyl or C_{1-6} alkoxycarbonyl group; a tetrahydropyranyl group; or a tetrahydrofuryl group.

3. The compound of claim 1 wherein R^1 is a phenyl, pyridyl or N-oxopyridyl group optionally having one or more substituents selected from the group consisting of halogen, C_{1-3} alkyl, C_{1-3} alkyl substituted with one or more halogen atoms, hydroxymethyl, acetoxymethyl, amino, cyclopropylamino, C_{1-3} alkylamino, di(C_{1-3} alkyl)amino, C_{1-4} alkoxy, hydroxy, cyano, nitro, carboxy, C_{1-4} alkoxycarbonyl,

carbamoyl, cyclopropylcarbamoyl, C_{1-4} alkylcarbamoyl and di(C_{1-4} alkyl)carbamoyl; R^2 is C_{1-6} alkyl; R^3 and R^4 are each independently hydrogen, halogen, cyano, nitro, amino, acetamido, trifluoroacetamido, C_{1-3} alkyl, C_{1-3} alkyl substituted with one or more halogen atoms or C_{1-3} alkoxycarbonyl; A is O or S; and Z is O, S, C=O or NH.

4. The compound of claim 3 wherein R^1 is a phenyl, pyridyl or N-oxopyridyl group optionally having one or more substituents selected from the group consisting of methyl, amino, nitro, methoxy, trifluoromethyl, fluoro, chloro, cyano, hydroxymethyl, acetoxymethyl, methoxycarbonyl and carbamoyl; R^2 is ethyl or isopropyl; R^3 and R^4 are each independently hydrogen, chloro, fluoro, methyl, fluoromethyl, trifluoromethyl or nitro; A is O; and Z is O, S, C=O or NH.

5. A process for the preparation of the compound of claim 1 which comprises coupling a compound of formula(II) with a compound of formula(III) in the presence of a base:



(II)

$$R^1\text{-}CH_2\text{-}Y \qquad \text{(III)}$$

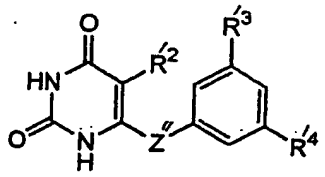
wherein:

R^1, R^2, R^3, R^4 and A have the same meanings as defined in claim 1;

Z' is same as Z defined in claim 1 with the proviso that when A is oxygen, it can be a acetamido group; and

Y is halogen, methanesulfonyl, toluenesulfonyl or trifluoromethanesulfonyl.

6. A compound having the formula(II):



(II)

wherein:

R'^2 is ethyl or isopropyl;

R'^3 is nitro, amino, acetamido, trifluoroacetamido or C_{1-3} alkoxycarbonyl;

R'^4 is methyl or halogen; and

Z" is C=O, NH or acetamido.

7. An antiviral composition comprising a therapeutically effective amount of the 2,4-pyrimidinedione compound or a pharmaceutically acceptable salt thereof of claim 1 as an active ingredient, and a pharmaceutically acceptable carrier and/or adjuvant.

INTERNATIONAL SEARCH REPORT

international application No. PCT/KR00/00166

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 239/04, A61K 31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimun documentation searched (classification system followed by classification symbols)

C07D 239/04, A61K 31/495

Documentation searched other than minimun documentation to the extent that such documents are included in the fileds searched

Korean Patents and applications for inventions since 1975

Electronic data base consulted during the intertnational search (name of data base and, where practicable, search trerms used)

WPI, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 07-165731(AJINOMOTO CO., INC.) 27 June 1995(27.06.1995), see entire document.	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevence; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 JUNE 2000 (15.06.2000)	19 JUNE 2000 (19.06.2000)

Name and mailing address of the ISA/KR	Authorized officer
Korean Industrial Property Office Government Complex-Taejon, Dunsan-dong, So-ku, Taejon Metropolitan City 302-701, Republic of Korea Facsimile No. 82-42-472-7140	LEE, Su Hyoung Telephone No. 82-42-481-5602

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR00/00166

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 07-165731	27.06.95	EP00649840	26.04.95
		US 5496824	05.03.96